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EXTRA-ADRENAL PHEOCHROMOCYTOMA (PARAGANGLIOMA) OF THE URINARY BLADDER: A CASE REPORT

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The case of a 49-year-old male patient with paraganglioma of the urinary bladder is presented here. The patient's only complaint was of gross hematuria: sustained hypertension and post-micturitional hypertension were not presented. Transurethral resection was performed to diagnose the bladder tumor. Pathological examination resulted in the diagnosis that the resected tissue was a paraganglioma. Computed tomography, magnetic resonance imaging and iodine-131-labeled metaiodobenzylguanidine scintigraphy revealed that the tumor was a primary paraganglioma in the urinary bladder. Plasma concentrations of the catecholamines were virtually within the normal limits. Hypertensive crisis was not revealed during the transurethral resection. The tumor was non-functional. Partial cystectomy was performed. The patient has remained disease-free for five months after surgery.

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Key words : Extra-adrenal pheochromocytoma (paraganglioma), Partial cystectomy, Urinary bladder

INTRODUCTION

The paraganglion system includes the adrenal medulla, carotid, aortic and vagal bodies, with a small group of cells associated with the cervical, thoracic and abdominal sympathetic ganglia. The paragangliomas were classified into pheochromocytomas arising from the adrenal medulla and extra-adrenal pheochromocytomas arising from other sites. Extra-adrenal pheochromocytoma is often referred to as paraganglioma in a narrow sense. The most common area of occurrence of extra-adrenal pheochromocytomas has been the superior para-aortic region (the region between the diaphragm and the inferior renal poles). Forty-six percent of extra-adrenal pheochromocytomas are located in the superior para-aortic region, and 10% of them in the urinary bladder¹⁾. Paraganglioma of the urinary bladder is rarely encountered. The primary involvement of the urinary bladder constitutes less than 0.06% of all vesical neoplasms²⁾. This is the 64th case of paraganglioma of the urinary bladder to be reported in the Japanese literature on Medline.

CASE REPORT

A 49-year-old male visited the Saku Central Hospital with complaints of gross hematuria. No other local or general symptomatology was present. His medical history and physical examination were unremarkable. Blood pressure was normal. On admission, cystoscopic examination revealed a solitary mass on the anterior wall of the bladder, covered by edematous urothelium (Fig. 1). Further the blood pressure of the patient on admission was



Fig. 1. Cystoscopic examination revealed a solitary mass on the anterior wall of the bladder, covered by edematous urothelium.

found to be 121/85. Admission laboratory values were within normal ranges; these include the complete blood count, blood urea nitrogen, creatinine, and serum electrolytes. Computed tomography revealed a strong contrast-enhanced mass on the anterior wall of the urinary bladder. Transurethral resection (TUR) was performed to arrive at a definitive diagnosis. The tumor bled more than a transitional cell carcinoma. During the surgery, the blood pressure and heart rate were stable. No hypertensive crisis was revealed.

Tumor cells were large and rich in granular matrix and were arranged in nests separated by a prominent fibrovascular stroma resembling normal adrenal medulla (Fig. 2). Immunohistochemical tests revealed that the tumor cells were strongly positive for

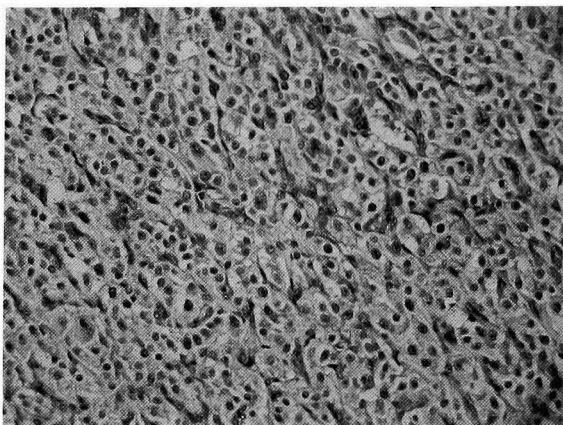


Fig. 2. Histopathological examination of the tumor specimen showed nests of round cells separated by delicate vascular stroma (H & E $\times 200$).

the neuroendocrine markers such as chromogranin A and synaptophysin. The findings were similar to those obtained for the carcinoid tumors, except that the sustentacular cells were positive for S-100 protein. The disease was histopathologically diagnosed as paraganglioma.

Plasma norepinephrine was found to be 567 pg/ml (normal, 420 pg/ml), while the plasma epinephrine and dopamine levels were found to be normal. The abdominal magnetic resonance image did not reveal a primary adrenal tumor. Iodine-131-labeled metaiodobenzylguanidine (^{131}I -MIBG) scintigraphy revealed a high uptake in the urinary bladder and a normal uptake in the adrenal gland (Fig. 3).

Partial cystectomy, including mass and pelvic lymph node dissection, was performed under general anesthesia. Preoperative medication such as α -blockers or β -blockers was not necessary, because the transurethral resection did not reveal a hypertensive crisis. During surgery, blood pressure and heart rate

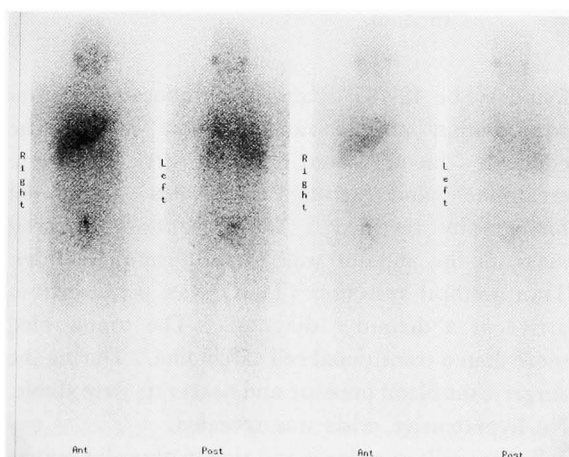


Fig. 3. Iodine-131-labeled metaiodobenzylguanidine (^{131}I -MIBG) scintigraphy revealed a high uptake in the urinary bladder and a normal uptake in the adrenal gland.

were stable despite pressurization by the fingers. The histopathological staging of the tumor was pT3a. The surgical margins were free of the tumor. The convalescence of the patient was uneventful.

DISCUSSION

The paraganglion system is a major component of the dispersed neuroendocrine system, which includes elements of both the central and the peripheral nervous system. The paraganglion system can be divided into the adrenal medulla which is an innervated neuroendocrine organ of primary importance in the orthosympathetic system and the extra-adrenal paraganglion system. This second system can be divided into two components: (1) One that is associated with the orthosympathetic system in the para-aortic, thoracic, and abdominal regions, which is functionally related to the adrenal medulla and (2) the other that is related to the parasympathetic system, which functions as a series of afferent receptor organs such as the carotid body. The structure of the paraganglion consists of chief cells and sustentacular cells. The chief cells are round or oval and contain neurosecretory granules that store catecholamines. The sustentacular cells are located on the periphery of the chief cells³.

Pheochromocytomas are known as 10% tumors in part due to the belief that 10% of these tumors arise at the extra-adrenal sites. However, this belief may lead to an underestimation of the problem. Raymond K et al.¹ reviewed the data for 243 cases in 19 reports and found that 18% of the pheochromocytomas had been determined at extra-adrenal locations. However, paragangliomas (extra-adrenal pheochromocytomas) are actually uncommon lesions, and paragangliomas of the urinary bladder are rare.

Pheochromocytomas of the urinary bladder also often cause hematuria and intermittent hypertension during micturition⁴. The present case did not have a past history of hypertension. Only a painless hematuria was present. The catecholamines and their metabolites in the blood and urine can be used to distinguish functional tumors from non-functional ones. Eighty-three percent of these tumors are hormonally active⁴. In this case, plasma concentrations of the catecholamines were virtually within the normal limits. The tumor was non-functional.

It is important to diagnose the cystoscopic findings. The tumor is usually a solid mass covered by mucosa, which may appear normal, hypervascular, or superficially ulcerated. The differential diagnosis includes rhabdomyosarcoma, hemangioma, leiomyoma, neurofibroma, and cystitis¹. Computed tomography, magnetic resonance imaging, and ^{131}I -MIBG scintigraphy can be used to locate the tumor⁵.

Shapiro et al.⁶⁾ reported the accuracy of I-MIBG on symptomatic pheochromocytoma (sensitivity 87.4%, specificity 98.9%). Maurea et al.⁷⁾ reported that I-MIBG focal-increased uptake by adrenal lesions was observed in all 15 patients with pheochromocytoma and ganglioneuroma, and for 5 cases of these 15 cases, catecholamine hyperproduction was not observed. I-MIBG can be used to diagnose non-functional pheochromocytomas as in the present case. Hwang et al.⁸⁾ reported that, as part of preoperative imaging methods, positron emission tomography (PET) using 6-[¹⁸F] fluorodopamine may help precisely localize all involved tissues.

The histopathological findings are very similar to those of the normal adrenal medulla. Further, the immunohistological findings are important for diagnosis. The chief cells of the tumor have immunoreactivity to neuroendocrine markers such as chromagranin A and synaptophysin, whereas the sustentacular cells of paragangliomas have immunoreactivity to the S-100 protein³⁾

It is difficult to histopathologically diagnose paraganglioma as malignant or benign. The clinical staging of paraganglioma of the urinary bladder can be classified in a similar manner as that of urothelial cancer. The TNM staging can be used for this purpose⁹⁾. Pathological T classification is an important prognostic factor of paraganglioma. Liang and Bradley et al.¹⁰⁾ reported that patients who suffer from paraganglioma of the advanced classification ($\geq T3$) are at a risk of recurrence, metastasis and death due to the disease, whereas patients with the T1 or T2 classification of the disease had favorable outcomes after complete tumor resection.

Paragangliomas in the urinary bladder require partial or, less often, total cystectomy. Total cystectomy is often performed in the case of pelvic lymphadenopathy. In addition, pelvic lymph node dissection has been recommended to exclude metastatic disease for all cases of paragangliomas in the urinary bladder. Transurethral resection is an optional form of treatment, but in the case of invasion of muscular layer witnessed in the present case, transurethral resection cannot be recommended because of the risk of local recurrence of the residual tumor⁴⁾.

A long-term follow-up of these patients is important

since, at present, it is not histopathologically feasible to differentiate a benign pheochromocytoma from a malignant pheochromocytoma. Sequential monitoring of blood pressure and of catecholamines and their metabolites in the blood and urine can be used to follow-up of these patients. In a non-functional tumor such as in the present case I-MIBG scintigraphy can also be used in the follow-up patients.

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和文抄録

膀胱内に発生した傍神経節腫の1例

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膀胱内に発生した傍神経節腫の1例を経験したので報告する。49歳，男性，肉眼的血尿を主訴に来院した。持続する高血圧や排尿後の高血圧は認められなかった。膀胱鏡にて腫瘍を認め，経尿道的膀胱腫瘍切除術を施行した。切除標本の病理診断は傍神経節腫であった。CT，MRI，I-131-MIBG シンチグラフィーを施

行し，膀胱原発の傍神経節腫を認めた。血中のカテコラミンはほぼ正常範囲内であり，経尿道的膀胱腫瘍切除術中に高血圧発作を起こすことはなく，非機能性の傍神経節腫であった。膀胱部分切除術を施行した。術後5カ月経過したが，再発を認めていない。

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